Behavioral and Neurophysiological Markers of ADHD in Children, Adolescents, and Adults: A Large-Scale Clinical Study

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Marionna Münger[1], Gian Candrian[2], Johannes Kasper[3], Hossam Abdel-Rehim[4], Dominique Eich[1], Andreas Müller[2], and Lutz Jäncke[1,5]

Abstract

This study aimed to re-evaluate the possible differences between attention-deficit/hyperactivity disorder (ADHD) subjects and healthy controls in the context of a standard Go/NoGo task (visual continuous performance test [VCPT]), frequently used to measure executive functions. In contrast to many previous studies, our sample comprises children, adolescents, and adults. We analyzed data from 447 ADHD patients and 227 healthy controls. By applying multivariate linear regression analyses, we controlled the group differences between ADHD patients and controls for age and sex. As dependent variables we used behavioral (number of omission and commission errors, reaction time, and reaction time variability) and neurophysiological measures (event-related potentials [ERPs]). In summary, we successfully replicated the deviations of ADHD subjects from healthy controls. The differences are small to moderate when expressed as effect size measures (number of omission errors: $d = 0.60$, reaction time variability: $d = 0.56$, contingent negative variation (CNV) and P3 amplitudes: $-0.35 < d < -0.47$, ERP latencies: $0.21 < d < 0.29$). Further analyses revealed no substantial differences between ADHD subtypes (combined, inattentive, and hyperactive/impulsive presentation), subgroups according to high- and low-symptomatic burden or methylphenidate intake for their daily routine. We successfully replicated known differences between ADHD subjects and controls for the behavioral and neurophysiological variables. However, the small-to-moderate effect sizes limit their utility as biomarkers in the diagnostic procedure. The incongruence of self-reported symptomatic burden and clinical diagnosis emphasizes the challenges of the present clinical diagnosis with low reliability, which partially accounts for the low degree of discrimination between ADHD subjects and controls.

Keywords

attention-deficit hyperactivity disorder, ERP, VCPT, neurophysiology, biomarker

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Introduction

According to the Diagnostics and Statistical Manual of Mental Disorders, fifth edition (DSM-5), ADHD is a developmental disorder characterized by inappropriate levels of attention and limitations in executive functioning. Although symptoms may alter over the lifespan, functional impairment persists for many individuals into adulthood.[1,2] Since the clinical diagnosis of ADHD has shown only moderate reliability, validity, and objectivity, research is trying to identify behavioral and neurophysiological markers to complement the current diagnostic procedure and to improve the understanding of the neural underpinnings of ADHD.[3-5]

A frequently used behavioral paradigm is the VCPT, a classical Go/NoGo task. This paradigm assesses executive functions, including sustained attention, alertness, and inhibition. Most studies using such paradigms report reduced cognitive performance of subjects with ADHD,[6-11] such as increased omissions and commission errors.[9,12] The number of commission errors is often referred to as a lack of inhibitory control or impulsivity, whereas the number of omission errors is associated with inattention.[13] The most robust behavioral measure discriminating ADHD and control subjects is reaction time variability, which is mostly larger in ADHD subjects.[11,14,15]

[1]University of Zürich, Zürich, Switzerland
[2]Brain and Trauma Foundation Grisons, Chur, Switzerland
[3]Praxisgemeinschaft für Psychiatrie und Psychotherapie, Lucerne, Switzerland
[4]Psychiatrie und Psychotherapie Rapperswil, Rapperswil, Switzerland
[5]University Research Priority Program (URPP) "Dynamics of Healthy Aging", Zurich, Switzerland

Corresponding Author:
Marionna Münger, Department of Neuropsychology, University of Zürich, Zürich, Switzerland.
Email: marionna.muenger@uzh.ch

Furthermore, alterations in executive functions are reflected by deviating neurophysiological processing of the perceived stimuli, represented by the amplitude and latency of the ERPs. Subjects with ADHD show generally attenuated amplitudes and increased latencies in several positive and negative deflections.[4,16-18]

These behavioral and neurophysiological measures are often used as biomarkers to identify ADHD subjects. On an individual level, they provide valuable information about neuronal processing and executive functions.[19,20] For example, P3 deflections are related to attentional resources and reorientation,[21] whereas the late CNV reflects task-set representation[22] and anticipatory attention.[23] The NoGo and Go trials' ERP difference curve was associated with conflict detection (N2d) and inhibition of action (P3d).[16,24]

In this study, we are re-evaluating the question, whether and how strong typical behavioral and neurophysiological metrics of executive functions differ between subjects diagnosed as ADHD and healthy controls. We hypothesize that ADHD subjects will demonstrate an increased number of errors, increased reaction time variability, attenuated ERP amplitudes, and increased ERP latencies. A particular aspect of our study is the large cohort of over 650 subjects, comprising children, adolescents, and adults. With this large sample, we are in a position to compute robust statistical metrics for group differences between ADHD and controls, and investigate the potential interaction of group and age categories.

Methods

Subjects robust

Data were taken from a large-scale multicenter clinical study that includes n = 447 ADHD patients and n = 227 healthy controls (total number of available subjects: n = 674). The subjects' age range is 6 to 60 years (mean and standard deviation: 19.0 ± 13.8 years). Overall, n = 212 children aged 6-13 years (ADHD: n = 149; 10.2 ± 1.7 years; controls: n = 63, 9.9 ± 1.7 years), n = 107 adolescents aged 13-18 years (ADHD: n = 88; 14.9 ± 1.4 years; controls: n = 19, 16.6 ± 1.6 years), and n = 355 adults (ADHD: n = 210; 34.4 ± 10.1 years; controls: n = 145, 28.8 ± 11.9 years) were included.

Data were collected in 2014 and 2015 as the baseline assessment of a longitudinal project lasting 2 years. The ADHD subjects were diagnosed by certified psychiatrists and clinical psychologists according to the DSM-5. Fluid intelligence was assessed by the standard IQ paper and pencil test (<9 years, CFT 1-R[25]; 9-16 years, CFT 20-R part I[25]; >16 years, WMT-2[26]). General exclusion criteria for the study were traumatic brain injury, loss of consciousness in the past, another primary mental disorder (e.g., depression and schizophrenia), drug abuse, pregnancy, epilepsy, and an IQ < 80. The participants had to be able to follow the study instructions in German and provide informed consent. All subjects have been medication-free on the day of the assessment. However, n = 139 (31%) of the ADHD subjects took methylphenidate comprising medication for their daily routine (e.g., Ritalin, Concerta, Elvanse). Hundred and ninety-two subjects did not use methylphenidates (n = 192, 43%), while for n = 116 (26%) information was missing.

Descriptive information of the subjects is shown in Table 1. The female-to-male (f/m) ratio is higher in the control than in the ADHD group (f/m controls = 1.41; f/m ADHD = 0.51; the odds ratio for this difference is 2.8, 95% confidence interval [CI] = [2, 3.9]). The subjects of the two groups were on average of similar age ($t[672] = 1.82$, $P = .07$); however, they differ in terms of IQ scores ($t[654] = 654$, <0.01, $d = -0.41$ 95% CI = [−0.58, −0.25]).

Subjects with <40% of valid trials (artifact-free electroencephalography [EEG] and no errors) were excluded (n = 55 ADHD and n = 4 controls), resulting in a reduced sample for all ERP-related analyses (n = 432, ADHD and n = 224 controls). ADHD subjects had less valid trials compared to the controls under Go and NoGo conditions. Median valid trials and interquartile ranges under the Go condition were 70 [63, 81] for the control and 60 [50, 73] for the ADHD group ($W = 68001$, $P < .01$, $r = 0.2$ 95% CI = [0.28, 0.35]). Under the NoGo condition, the values were 84 [79, 92] for the control and 76 [67, 87] for the ADHD group ($W = 67185$, $P < .01$, $r = 0.2$ 95% CI = [0.26, 0.34]).

As the ADHD clinical diagnosis shows a low reliability,[27-29] we cross-checked it with the self-reported questionnaire data of ADHD symptoms of the DSM-5.[30,31] Symptoms experienced "often" or "very often" were dummy coded with 1 and subsequently summed up within the two subscales: (1) *inattention* and (2) *hyperactivity and impulsivity*. Congruence of the self-reported questionnaire with the clinical diagnosis was achieved if a subject exceeded the threshold of 6 in children, respectively, 5 in adults within one subscale, as determined by the DSM-5 as a requirement for the diagnosis of ADHD.[31] Based on the congruence (yes vs no) between the clinical diagnosis and the self-report data, we subdivided the ADHD group into two subgroups: ADHD-1 (yes; n = 346, 77%) and ADHD-2 (no; n = 101, 23%). Please note that certified clinicians diagnosed all ADHD subjects at the entry of the study. We determined the ADHD subtype for

Table 1. Demographic Characteristics of the Dataset. The Number of Male and Female Subjects, and the Means and Standard Deviations for Age, and IQ are Given.

	Control	ADHD
n total	**227**	**447**
n (%) female	133 (59%)	151 (34%)
n (%) male	94 (41%)	296 (66%)
Age (years)	20.6 ± 14.1	16.8 ± 13.7
IQ	109 ± 13	102 ± 15

Note: Missing data for IQ: control n = 3, ADHD, n = 15.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

all ADHD subjects with questionnaire data corresponding to the clinical diagnosis (n = 346); subjects exceeding the threshold in both subscales (ADHD-combined = 131, 38%), only in the inattention subscale (ADHD-inattention = 190, 55%), and only in the hyperactivity/impulsivity subscale (ADHD-hyperactivity/inattention = 25, 7%).

VCPT (Go/NoGo task)

We used a cued Go/NoGo task to assess executive functions, particularly challenging the sustained attention and inhibitory control. This task was used in a set of previous studies.[10,20,32,33] The test compromises 400 trials, of which each consists of a pair of consecutively presented visual stimuli (animals, plants, and humans). In Go-trials (animal–animal), a picture of an animal is followed by a picture of an animal, and the participant is asked to press a button. Failure of this task results in an omission error. In NoGo trials (animal–plant), the participant is asked to withhold from pressing the button. Failure of this task results in a commission error. Under the two ignore conditions (plant–plant and plant–human), no action is required. Each category was presented equally often (each 25%). Stimulus 1 was presented at 300 ms and stimulus 2 at 1400 ms (inter-stimulus interval = 1000 ms), each for 100 ms. Reaction time variability was computed for all Go trials, defined as the coefficient of variance for reaction time (standard deviation of mean reaction time divided by mean reaction time).

Electrophysiology

EEG data were recorded with the NeuroAmp® ×23, a 19-channel EEG system with a 24-bit resolution and a sampling rate of 500 Hz, which was down-sampled to 250 Hz. The input signals were bandpass filtered between 0.5 and 50 Hz. The montage was changed from linked earlobes to common average reference before processing. Electrodes were placed according to the International 10-20 system using a fitting electrode cap with tin electrodes (Electro-cap International Inc.). Impedance was kept below 5 kΩ for all electrodes. Raw EEG was recorded using the ERPrec software (BEE Medic GmbH) and processed as well as analyzed using Matlab-based in-house software. Eye blinks and horizontal eye movements were detected using independent component analysis decomposition and removed from EEGs by zeroing the activation of the respective components.[34] The remaining artifacts were removed by rejecting filtered EEG segments with amplitudes >100 μV and/or excessive activity in the 0-3 and 20-50 Hz frequency bands (threshold = channel *z*-score of 6).

ERPs

ERP features were extracted using a Matlab-based custom-built EEGLAB plug-in. After baseline correction using the 100 ms pre-stimulus period, the peak detection of the ERP components was determined within the adjusted time windows for three age groups: children (<13 years), adolescents (13-18 years), and adults (≥18 years). The point on the ERP waveform at which it reaches the maximum (or minimum) was determined within a time window whose size was set to 80% of the time interval between the component peak of interest and the preceding peak. For example, if P3 is at 300 ms and N2 at 200 ms, the window for P3 is fixed from 260 to 340 ms. The problem of inter-individual temporal differences was dealt with by using self-modeling warping functions.[35] The required minimum number of valid trials (no artifacts and no errors) is 40 within one condition, hence 40%. Applying this protocol, we calculated the amplitudes and latencies of the following ERP metrics: (1) the P3 after the Go-stimulus (GoP3), (2) the P3 after the NoGo-stimulus (NoGoP3), and (3) the N2 after the NoGo stimulus (NoGoN2). We also calculated the ERP metrics of the difference waves between NoGo and Go trials: (4) P3d and (5) N2d. The (6) CNV amplitude was defined in the 100 ms window prior to the second stimulus, by the area under the curve divided by the window size. NoGoP3, NoGoN2, CNV, P3d, and N2d were measured on electrode Cz and GoP3 at Pz.

Statistical analysis

The dependent variables for this analysis are the four behavioral measures (omission errors, commission errors, mean reaction time, and reaction time variability), as well as the amplitudes and latencies of the ERPs (GoP3, NoGoP3, NoGoN2, CNV, P3d, and N2d, without latency for CNV—thus in total 11 variables). We computed multiple linear regressions with the independent variables *group*, *age*, *age category*, *sex*, and the interactions between *age* × *age category* and *group* × *age category* for all dependent variables. The three categorical variables were defined as *age category* (children, adolescents, and adults), *sex* (female vs male), and *group* (ADHD vs controls). For the number of errors, we applied a log transformation to reduce skewness. The group differences between ADHD and controls are described by the multiple regression models' post-hoc tests, based on the *group* estimates and the residual standard error of the model. Therefore, the reported effect sizes for these group comparisons are controlled for age and sex. To estimate the relative importance of each independent variable in explaining the dependent variable, we used the *relaimpo* software tool in R using the *lmg* metric, providing a decomposition of the total variance explained by the model into non-negative contributions of each independent variable.[36] The necessary assumptions for applying linear regressions (ie, the approximately normal distribution of the residuals) were confirmed for the present dataset. All statistical analyses were carried out with routines from the R software[37] on an iMac. Since statistical tests using such large samples are anti-conservative revealing significant results ($P < .05$) even for very small effects, we use effect size measures (Cohen's d or relative importance) to interpret the results. In this context,

$d > 0.2$ or $R^2 > 1\%$ is considered as small, $d > 0.5$ or $R^2 > 9\%$ as moderate, and $d > 0.8$ or $R^2 > 25\%$ as large.[38]

Results

Mean ERP curves in the Go and NoGo condition are displayed in Figure 1. In addition, the corresponding difference curve and the CNV curve are shown.

We computed multiple linear regressions for each dependent variable of interest, with the *group*, *gender*, *age*, and *age category*, as independent variables, including the interactions: *age* × *age category* and *group* × *age category*. With this initial multiple regression (full model), we identified significant interactions between *group* and *age category* for only three measures: (1) the number of commission errors ($P < .001$), (2) the mean reaction time ($P = .001$), and (3) the latency of NoGoN2 ($P = .022$); details of group differences within the age categories are summarized in the supplementary Table S1. Since these regressions uncovered that the *group* × *age category* interactions are mainly negligible, we calculated multiple regression without this interaction (reduced model). The effect sizes as indicators of the relative importance of the independent variables are shown in Table 2.

As can be seen from Table 2, all multiple regressions were significant ($P < .05$), but substantially differ for the explained total variances from 3% to 57%. All age-related variables together (*age*, *age category*, and their interaction) explain the largest part of the variance, whereas *sex* explains maximally 1%.

The estimates of the independent variables and the results of the post-hoc tests for *group* are listed in Table 3. There is evidence that ADHD subjects commit more omission and commission errors than controls, present larger variability in the reaction times, and have attenuated amplitudes and longer latencies in most of the investigated ERP measures (exception: NoGoN2 and N2d amplitude). For an overview of the effect sizes, see Figure 2. Effect sizes (Cohen's d) reflect the magnitude of difference between ADHD subjects and controls; a

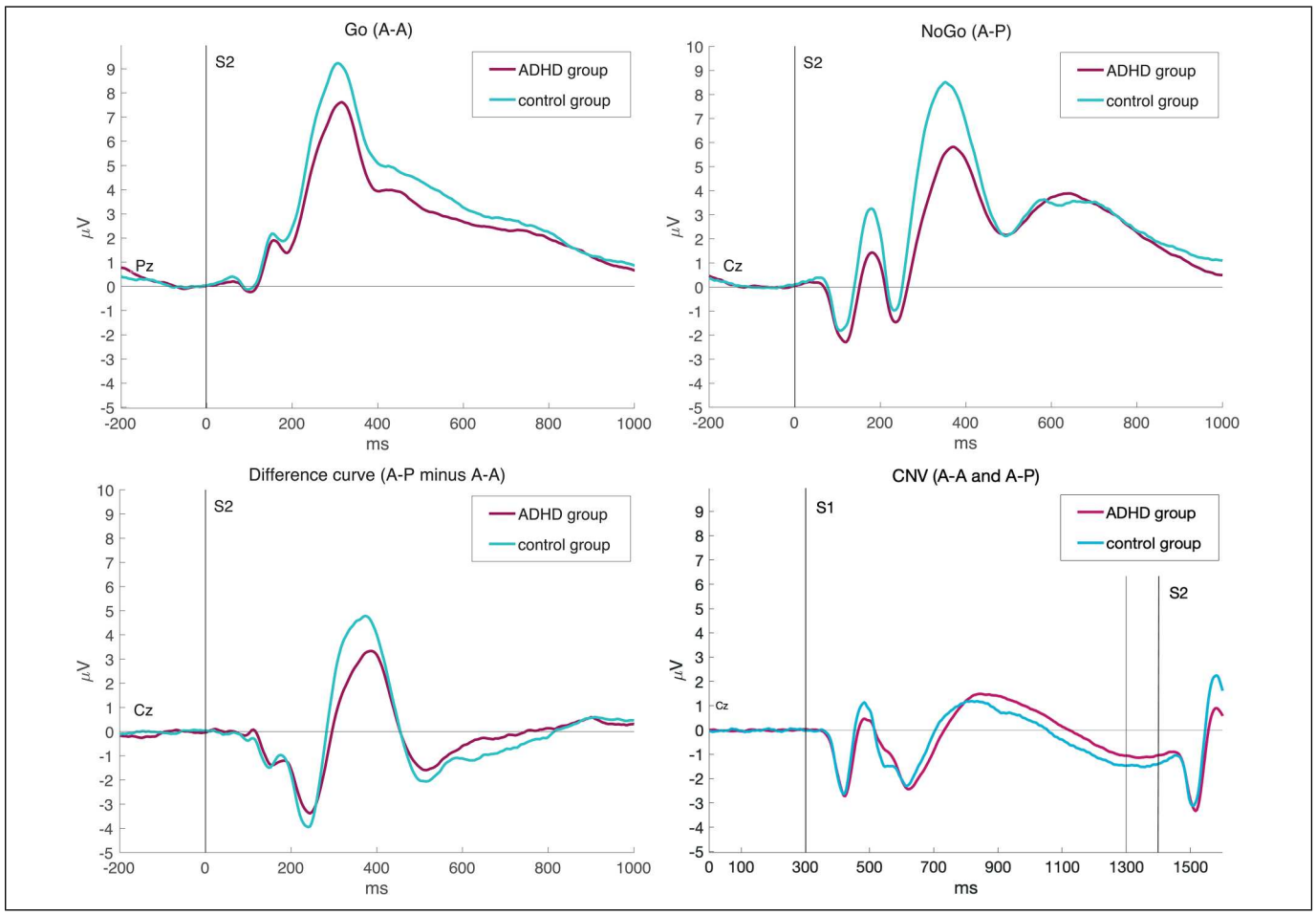

Figure 1. ERP curves for the ADHD and control group. The ERPs after the second stimulus (S2) under the Go (animal−animal) and NoGo conditions (animal−plant), as well as the difference curve, are shown. In addition, the CNV after the first stimulus (S1) under the Go and NoGo conditions is displayed.
Abbreviations: ERP, event-related potential; ADHD, attention-deficit/hyperactivity disorder.

Table 2. Summary of R^2 (As a Percentage of Explained Variance) for the Reduced Model (R^2 Total) and the R^2 Values Estimated with Relaimpo Separately for Each Independent Variable.

		Relative importance				
	R^2 total (%)	Sex (%)	Age (%)	Age cat (%)	Age × age cat (%)	Group (%)
Behavioral outcome measures						
Omission errors	37*	1	<1	26	5	6
Commission errors	19*	1	<1	13	<1	5
Reaction time	20*	<1	<1	14	5	<1
Reaction time variability	33*	2	<1	24	1	6
ERP amplitudes						
GoP3	29*	1	5	19	1	3
NoGoP3	12*	<1	1	4	2	4
NoGoN2	31*	1	3	25	1	1
CNV	3*	<1	<1	1	<1	2
P3d	5*	1	1	1	<1	3
N2d	31*	1	5	24	<1	<1
ERP latencies						
GoP3	5*	<1	1	2	<1	1
NoGoP3	50*	1	1	39	8	1
NoGoN2	57*	1	<1	44	11	1
P3d	27*	<1	2	19	4	1
N2d	8*	1	<1	3	1	2

Note: The number of omission and commission errors are transformed by log(number of errors + 1). The R^2 values are rounded to integer values. Abbreviations: Age cat, age category (children, adolescents, and adults); Age × age cat, interaction between age and age category; ERP, event-related potential; GoP3, P3 after the Go-stimulus; NoGoP3, P3 after the NoGo-stimulus; NoGoN2, N2 after the NoGo stimulus, P3d and N2d, difference curve between the NoGo and Go stimulus. *$P < .05$.

positive value in the behavioral measures indicate more errors and larger reaction time variability for ADHD subjects compared to controls, negative values for the ERP amplitudes indicate attenuated amplitudes for the ADHD subjects compared to controls and positive values for the ERP latencies indicate longer latencies for the ADHD subjects compared to controls.

Developmental effects are described by the estimates of the age-related variables in Table 3. The influence of *sex* on the dependent variables is very small (either 1% or below 1%). Male subjects showed slightly decreased GoP3 and increased N2d amplitude, and slightly increased GoP3 and N2d, and decreased P3d latency.

Additional exploratory regression analyses

We conducted subsequent exploratory regression analyses to examine the influence of additional independent variables on the outcome measures, which were available only for a subsample of the dataset. These analyses are based on the reduced model we have used for our main analysis.

In the first set of subsequent regressions, we added IQ as a further independent variable. This analysis revealed basically the same results as the original analyses. The relative importance of IQ on the dependent variables was small (for the number of omission errors: 3%; reaction time: 2%; NoGoP3 amplitude: 2%; P3d amplitude: 1%; others: <1%). A higher IQ was associated with a slightly lower number of omission errors (intercept = 3.23; IQ: $\beta = -0.01$; $P < .001$), shorter mean reaction times (intercept = 546; IQ: $\beta = -0.84$; $P < .001$), and increased NoGoP3 and P3d amplitudes (NoGoP3: intercept = 5.15, IQ: $\beta = 0.04$, $P = .006$ and P3d: intercept = 5.35, IQ: $\beta = 0.03$, $P = .025$).

The second set of subsequent regressions was performed exclusively with the subjects of the ADHD group, using *methylphenidate intake* in daily life as an additional independent variable. The explained variance of *methylphenidate* intake (categorical variable: yes = 1, no = 0) was <1% for all dependent variables and there was no evidence that the two subgroups do differ in any of the behavioral or neurophysiological outcome measures (all $P > .05$).

The next set of regressions, with a three-level *group* variable (ADHD-1, ADHD-2, and controls) did not generally change the results compared to our main analysis (amount of explained variance for *group* and *age category* was maximally 1%). The results of the post-hoc group comparisons are shown in the supplementary Table S2. The effect sizes between controls to ADHD-1, and controls to ADHD-2 were similar for reaction time variability. For the number of omission errors and the attenuation of GoP3, NoGoP3, NoGoN2, and CNV amplitude, the effect was slightly larger for ADHD-1 compared to controls, than for ADHD-2 compared to controls. For the P3d amplitude and N2d latency, the effect was descriptively larger between ADHD-2 and controls than between ADHD-1 and controls. There is no evidence for any difference in the direct comparison between ADHD-1 and ADHD-2.

For the fourth set of subsequent analyses, we subdivided the ADHD subjects into the three ADHD subtypes proposed by the DSM-5 (ADHD-combined, ADHD-hyperactivity/impulsivity, and ADHD-inattention). This regression analyses within the ADHD subjects revealed evidence for a small influence of subtype on some of the dependent variables (maximally 2%). Post-hoc comparisons between subtypes (see Table S3) revealed only two significant differences, namely reduced reaction time variability in ADHD-inattention compared to ADHD-combined ($t[337] = -3.17$, $P = -.005$, $d = -0.37$, 95% CI = [−0.60, −0.14]) and reduced GoP3 latency in ADHD-inattention compared to ADHD-hyperactivity/inattention ($t[294] = 2.37$, $P = .049$, $d = -0.55$, 95% CI = [−1.01, −0.09]).

Discussion

The present study re-evaluates whether ADHD subjects and healthy control differ in a standard psychological test paradigm examining executive functions, assessed by a VCPT in association with ERPs. We successfully replicated often reported

Table 3. Summary of the Coefficients Obtained from the Multiple Regression Analysis (Reduced Model). The Intercepts, the Estimates Separately for Each Independent Variable, and the Group Contrast ADHD versus Control are Given.

		Regression estimates								Group contrast		
		Intercept	Age cat		Age × age cat			Sex	Group	ADHD vs control		
	R^2 total (%)	Child	Adol vs child	Adults vs child	Age child	Age adol	Age adults	Male	ADHD	*t* ratio	*P*-value	Cohen's *d*
Behavioral outcome measures												
Omission errors	37*	1.86*	−0.68*	−1.29*	−0.24*	0.15*	0.24*	−0.1	0.53*	−7.00	<.001*	0.60*
Commission errors	19*	0.79*	−0.28*	−0.62*	0.01	−0.05	−0.01	0.03	0.35*	−5.74	<.001*	0.49*
Reaction time (ms)	20*	453*	−71*	−78*	−21*	15*	22*	−6	7	−0.99	.323	0.08
Reaction time variability	33*	0.28*	−0.01	−0.08*	0.01*	−0.01*	−0.01*	0	0.04*	−6.61	<.001*	0.56*
ERP amplitudes												
GoP3	29*	13.63*	−1.18*	−4.42*	0.31*	−0.61*	−0.43*	−0.81*	−1.72*	5.39	<.001*	−0.47*
NoGoP3	12*	9.83*	2.37*	2.22*	0.68*	−0.22	−0.76*	−0.4	−2.41*	5.03	<.001*	−0.44*
NoGoN2	31*	−5.28*	2.32*	4.2*	0.47*	−0.06	−0.39*	−0.09	−0.54	1.96	.051	−0.17
CNV	3*	−1.4	0.01	−0.18	−0.04	0.12	0.04	0.04	0.36*	−2.96	<.001*	0.26*
P3d	5*	8.53*	−0.09	−1.21*	0.13	−0.45	−0.17	−0.76	−1.53*	3.95	<.001*	−0.35*
N2d	31*	−8.22*	1.87*	3.94*	0	0.26	0.09	1.0*	0.21	−0.86	.389	0.08
ERP latencies												
GoP3	5*	296*	7*	12*	−1*	4*	2*	6*	8*	−2.38	.017*	0.21*
NoGoP3	50*	404*	−68*	−61*	−13*	10*	14*	0	10*	−3.30	<.001*	0.29*
NoGoN2	57*	284*	−51*	−55*	−13*	10*	13*	1	6*	−2.84	<.001*	0.25*
P3d	27*	397*	−47*	−41*	−9*	8*	10*	−3*	8*	−2.41	.016*	0.21*
N2d	8*	245*	−12*	−10*	−3*	4*	4*	7*	8*	−3.12	<.001*	0.27*

Note: For the categorical variables group, sex, and age category, the standard procedure for generating dummy variables as provided by the lm package was used and the number of errors are transformed by log(number of errors + 1). For the group contrasts ADHD versus controls Cohen's *d* effect sizes are averaged over age categories and sex. Positive effect sizes for negative deflections in the ERP curve (NoGoN2, CNV, and N2d) reflect attenuated ERP amplitudes in ADHD. Negative effect sizes for positive deflections in the ERP curve (GoP3, NoGoP3, and NoGoN2 and P3d) reflect attenuated ERP amplitudes in ADHD. Details for the variables with evidence for an interaction of group and age category (number of commission errors, reaction time, and NoGoN2 amplitude) are described in the supplementary Table S1.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; Age cat, age category (children, adolescents, and adults); Age × age cat, interaction between age and age category; ERP, event-related potential; GoP3, P3 after the Go-stimulus; NoGoP3, P3 after the NoGo-stimulus; NoGoN2, N2 after the NoGo stimulus; P3d and N2d, difference curve between the NoGo and Go stimulus. *$P < .05$.

differences, namely increased number of errors, larger reaction time variability, attenuated ERP amplitudes, and increased ERP latencies in ADHD subjects compared to controls.

The magnitude of these group differences, controlled for age, was small to moderate with effect sizes ranging between $d = 0.2$ and $d = 0.6$. These group differences were comparable across all age categories, except for the number of commission errors, mean reaction time, and NoGoN2 latency. Furthermore, the exploratory analysis showed that ADHD subtypes (ADHD-combined, ADHD-inattention, and ADHD-hyperactivity/inattention), and ADHD patients with high and low self-reported ADHD burden (ADHD-1 and ADHD-2) do generally not differ in the assessed variables. Furthermore, ADHD subjects taking methylphenidate for their daily routine did not differ from methylphenidate naive subjects in any behavioral or neurophysiological outcome measure during the medication-free assessment. A further finding of our analyses is that higher IQ scores are associated with slightly fewer omission errors, shorter mean reaction time, and larger NoGoP3 and P3d amplitudes.

The small-to-moderate differences between ADHD subjects and healthy controls in our large sample are basically congruent with the literature.[4,9,11,12,15] We successfully replicated group differences in this heterogeneous sample, comprising a large age range, ADHD subjects with different ADHD subtypes, medication intake, and symptomatic burden. Noteworthy, the data were collected within a clinical setting with limited experimental control.

We identified generally larger group differences for the behavioral, than for the ERP measures. The largest effect sizes were found for the number of omission errors ($d = 0.60$) and reaction time variability ($d = 0.56$), which are similar as reported in the previous meta-analyses (number of omission errors: Cohen's $d = 0.67$[12] and reaction time variability: Hedge's $g = 0.71$[15]). Reaction time variability and omission errors are supposed to reflect inconsistency in task performance and a lack of attentional control;[15,39] two major psychological deficits from which ADHD subjects suffer. Thus, such behavioral measures reflect ADHD deficiencies to a certain degree.

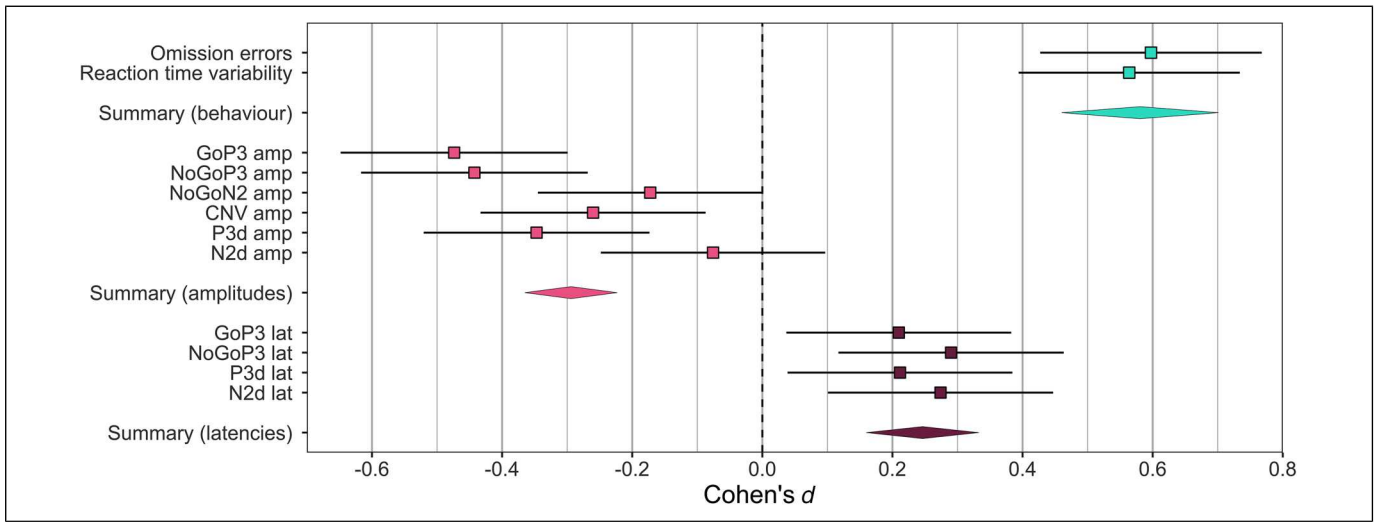

Figure 2. Overview of effect sizes for the behavioral and ERP-related measures. Cohen's *d* reflects the magnitude of difference between ADHD subjects and controls.

Note: Measures with significant interaction of group × age category are not represented (number of commission errors, mean reaction time, and NoGoN2 latency).

Abbreviations: ERP, event-related potential; ADHD, attention-deficit/hyperactivity disorder; amp, amplitude; lat, latency.

Age category turned out to affect the number of commission errors and reaction time. We found differential effects for the three age categories. The group difference for commission errors was large for children ($d = 1.06$) and small for adults ($d = 0.25$). Increased commission errors are supposed to reflect a lack of inhibitory control,[12] a functional deficit that is associated with hyperactive and impulsive symptoms of ADHD. Interestingly, children with ADHD exhibited faster reaction times compared to controls ($d = -0.37$), whereas adults with ADHD exhibited slower reaction times compared to controls ($d = 0.31$). These age-dependent differences between ADHD and control subjects might be due to a maturational lag in ADHD subjects, particularly in frontal brain areas involved in controlling executive functions.[40,41]

ERP measures are frequently used as biomarkers for executive functions.[16,24,42] In our sample, we identified attenuated ERP amplitudes and partly increased ERP latencies in ADHD subjects compared to controls. The effect sizes for the group comparison of the amplitude measures are comparable to those reported in a very recent meta-analysis, showing a small-to-moderate effect for the NoGoP3, GoP3, P3d, and CNV.[4] In contrast to the meta-analysis of Kaiser,[4] we found a moderate group difference for the GoP3 amplitude, which was comparable in size to the group difference for the NoGoP3. The P3 deflections are mainly associated with the allocation of attentional resources, which are deficiently operating in ADHD subjects.[16,21,43]

Interestingly, our data also uncovered that higher IQ scores are associated with increased NoGoP3 and P3d amplitudes. We suspect that this indicates larger cognitive resources in subjects with higher IQ, indicating potential coping strategies for attentional deficits.[44,45] This is in line with the observed lower number of omission errors in subjects with higher IQ in our sample.

Subgroup analyses to address ADHD heterogeneity (methylphenidate intake, symptomatic burden, and ADHD subtypes) did not exhibit substantial subgroup differences.

We found that the neurophysiological characteristics and behavioral performance are comparable between subjects taking methylphenidate for their daily routine and medication-naive subjects. This comparison has to be differentiated from discontinuation studies, where subjects stopping stimulant intake show deleterious performance and well-being compared to the continuation group.[46,47] Details about other strategies to handle the ADHD symptoms, such as psychotherapy, neurofeedback, or other therapeutic options, are not known for the sample.

The incongruence between the self-reported symptomatic burden and the clinical diagnosis (ADHD-1 and ADHD-2) emphasizes the challenges in ADHD research: the clinical classification is far from being highly reliable and valid.[27,29]

This study has several limitations: First, the sample comprises unbalanced ADHD subtypes. Second, a subset of the subjects was pharmacologically treated in their daily life. Third, all subjects mainly lived in Switzerland, which might prevent comparability of our results with studies from other countries. Finally, we had to exclude more ADHD subjects than controls for the ERP analysis because of artifacts.

Taken together, we mainly replicated meta-analytic findings in showing that ADHD subjects and controls moderately differed in terms of behavioral and neurophysiological measures reflecting executive functions. Remarkably, this is a replication within a large clinical dataset compromising a large age range and a high heterogeneity within the ADHD group (ADHD

subtypes, symptomatic burden, and medication intake). The obtained normalized group differences in terms of effect size measures are small to moderate according to Cohen's classification. For example, assuming a normal distribution and a moderate effect of $d = 0.5$ implies a substantial overlap of 80% of the two groups. This demonstrates that none of the assessed measures are useful as a sole biomarker for diagnosing ADHD subjects. The low reliability and validity of the ADHD diagnosis limit the comparisons of group means between ADHD and healthy controls, especially of ERP measures—which reflect rather neurophysiological processing divergence than obvious symptoms or behavioral deviations. For a successful establishment of biomarkers in the clinical setting, we need more complex approaches, combining multiple neuronal and behavioral markers to distinguish ADHD and healthy controls.[20] However, as stated previously,[48] a single neurophysiological marker can reflect individual profiles of specific functional impairments, which possibly show only small differences, on the group level because of large inter-individual variance, in both ADHD and healthy controls. Moreover, the ERPs analyzed in this study may represent summations of hidden components, so that the decomposition of those deflections into latent components by blind source separation methods might enhance the effect sizes.[49]

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Author Contributions

MM processed the experimental data, performed the analysis and drafted the manuscript. GC collected data, processed the experimental data and reviewed the manuscript. JK and HAR collected data. DE and AM designed the project. LJ supervised the project, contributed to writing the manuscript and interpreting the results. All authors revised the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Five private clinics from different parts of Switzerland participated in data collection. The study was approved by the cantonal ethics committee of Zurich (LeitEKZH_2013-0327/EKNZ_2014_160).

ORCID iD

Marionna Münger https://orcid.org/0000-0002-0857-0310

Supplemental Material

Supplemental material for this article is available online.

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